

PB88-162185

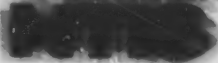
Health and Environmental
Effects Profile for Dinoseb

(U.S.) Environmental Protection Agency
Cincinnati, OH

Jan 84



U.S. Department of Commerce
National Technical Information Service



TECHNICAL REPORT DATA (Please read instructions on the reverse before completing)		
1. REPORT NO. EPA/600/X-84/322	2.	3. RECIPIENT'S ACCESSION NO. PB88-762185
4. TITLE AND SUBTITLE Health and Environmental Effects Profile for Dinoseb		5. REPORT DATE January 1984
		6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S)		8. PERFORMING ORGANIZATION REPORT NO.
9. PERFORMING ORGANIZATION NAME AND ADDRESS		10. PROGRAM ELEMENT NO.
		11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS Environmental Criteria and Assessment Office Office of Research and Development U.S. Environmental Protection Agency Cincinnati, OH 45268		13. TYPE OF REPORT AND PERIOD COVERED
		14. SPONSORING AGENCY CODE EPA/600/22
15. SUPPLEMENTARY NOTES		
16. ABSTRACT The Health and Environmental Effects Profile for <u>dinoseb</u> was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents. Quantitative estimates have been presented provided sufficient data are available. <u>Dinoseb</u> has been determined to be a systemic toxicant. An Acceptable Daily Intake (ADI), defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect, for <u>dinoseb</u> is 1×10^{-3} (mg/kg bw/day) for oral exposure. .001		
17. KEY WORDS AND DOCUMENT ANALYSIS		
A. DESCRIPTORS	B. IDENTIFIERS/OPEN ENDED TERMS	C. COSATI Field Group
18. DISTRIBUTION STATEMENT Public	19. SECURITY CLASS (This Report) Unclassified	21. NO. OF PAGES 65
	20. SECURITY CLASS (This page) Unclassified	22. PRICE A04 14.45

EPA/600/X-84/322
January 1984

HEALTH AND ENVIRONMENTAL EFFECTS PROFILE
FOR DINOSEB

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
CINCINNATI, OH 45268

DISCLAIMER

This document has been reviewed in accordance with U.S. Environmental Protection Agency policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEP's are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched."

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEP's will become part of the EPA RCRA docket.

ACKNOWLEDGEMENTS

The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3228 for U.S. EPA's Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa was the Technical Project Monitor and Helen Ball was the Project Officer. The final documents in this series were prepared for the Office of Solid Waste, Washington, DC.

Scientists from the following U.S. EPA offices provided review comments for this document series:

Environmental Criteria and Assessment Office, Cincinnati, OH
Carcinogen Assessment Group
Exposure Assessment Group
Reproductive Effects Assessment Group

Editorial review for the document series was provided by:

Judith Olsen and Erma Durden
Environmental Criteria and Assessment Office, Cincinnati, OH

Technical support services for this document series were provided by:

Bette Zwyer, Pat Daunt, Karen Mann, and Jacky Bohanon
Environmental Criteria and Assessment Office, Cincinnati, OH.

TABLE OF CONTENTS

	<u>Page</u>
1. INTRODUCTION.	1
1.1. STRUCTURE AND CAS NUMBER	1
1.2. PHYSICAL AND CHEMICAL PROPERTIES	2
1.3. PRODUCTION DATA.	3
1.4. USE DATA	3
2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES.	5
2.1. WATER.	5
2.2. AIR.	6
2.3. SOIL	6
3. EXPOSURE.	10
3.1. WATER.	10
3.2. FOOD	10
3.3. INHALATION	10
3.4. DERMAL	10
4. PHARMACOKINETICS.	12
4.1. ABSORPTION	12
4.2. DISTRIBUTION	13
4.3. METABOLISM	16
4.4. ELIMINATION.	17
5. EFFECTS	19
5.1. CARCINOGENICITY.	19
5.2. MUTAGENICITY	20
5.3. TERATOGENICITY	24
5.4. OTHER REPRODUCTIVE EFFECTS	27
5.5. CHRONIC TOXICITY	28
5.6. OTHER RELEVANT INFORMATION	29
6. AQUATIC TOXICITY	32
6.1. ACUTE EFFECTS.	32
6.2. CHRONIC EFFECTS.	35
6.3. PLANT EFFECTS.	35
6.4. RESIDUE.	36
6.5. OTHER RELEVANT INFORMATION	36

	<u>Page</u>
7. EXISTING GUIDELINES AND STANDARDS	37
7.1. HUMAN.	37
7.2. AQUATIC.	37
8. RISK ASSESSMENT	38
9. REFERENCES.	40
APPENDIX: LITERATURE SEARCHED.	54

LIST OF TABLES

<u>No.</u>	<u>Title</u>	<u>Page</u>
3-1	Dinoseb Contamination of Ontario Well Water, 1969-1978. . .	11
4-1	Dinoseb Recovery After 138 Days	14
4-2	Recovery of Dinoseb and Its Metabolites After Oral or Intraperitoneal Administration to Pregnant Mice	15
5-1	Mutagenicity Assays Performed With Dinoseb.	21
5-2	Interactions of Dinoseb With DNA or RNA	22
5-3	Teratogenicity of Dinoseb	25
5-4	Acute Lethal Toxicity of Dinoseb.	31
6-1	Acute Lethal Effects of Dinoseb to Freshwater Fish.	33

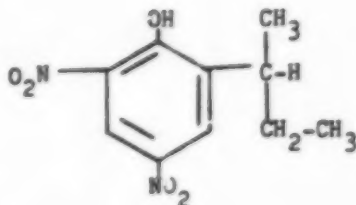
LIST OF ABBREVIATIONS

ACR	Acute-to-chronic toxicity ratio
ADI	Acceptable daily intake
BCF	Bioconcentration factor
CNS	Central nervous system
ECG	Electrocardiogram
EEG	Electroencephalogram
i.p.	Intraperitoneal
LC ₅₀	Concentrations lethal to 50% of recipients (and all other subscripted dosage levels)
LD ₅₀	Dose lethal to 50% of recipients (and all other subscripted dosage levels)
MATC	Maximum allowable threshold concentration
MEK	Methylethyl ketone
ppb	Parts per billion
ppm	Parts per million
RNA	Ribonucleic acid
s.c.	Subcutaneous
UV	Ultraviolet

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Dinoseb is the common name for 2-sec-butyl-4,6-dinitrophenol. Current Chemical Abstract usage is 2-(1-methylpropyl)-4,6-dinitrophenol. Other chemical synonyms include 2,4-dinitro-6-sec-butylphenol, 2,4-dinitro-6-(1-methyl propyl)phenol, 4,6-dinitro-2-(1-methyl-n-propyl)phenol, dinitrobutylphenol and s,4-dinitro-6-sec-butylphenol. Dinoseb was developed by the Dow Chemical Company under the code number "DN289" and trademark "Premerge" (BCPC, 1977). Other commercial trade names for dinoseb include "Basanite," "Caldon," "Gebutox," "Sinox" and "Subitex" (Ouellette and King, 1977). Additional synonyms for dinoseb or its formulations include Aatox, Aretit, Butaphene, BNP20, BNP 30, Chemox PE, Dibutox, Dinitrall, dinosch, dinosebe, DNBP, DNOSBP, DNSBP, Elgetol, ENT 1122, Kiloseb, Nitropone C, Phenotan, Sparic and Spurge. The structure and empirical formula for dinoseb are as follows:



Empirical formula: $C_{10}H_{12}N_2O_5$

Molecular weight: 240.2

The Chemical Abstract Services (CAS) Registry number for dinoseb is 88-85-7.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Dinoseb is a dark brown solid or dark orange liquid (of 95-98% purity), depending upon temperature, with a pungent odor (WSSA, 1979; BCPC, 1977).

Selected physical properties are as follows:

Melting point:	
technical product	30-40°C (BCPC, 1977)
pure product	38-42°C
Specific gravity:	
	1.29 at 30°C (Verschueren, 1983)
	1.265 at 45°C (WSSA, 1979)
Boiling point:	
	not determined, flash point 177°C (WSSA, 1979)

Vapor pressures (WSSA, 1979):

<u>Temperature, °C</u>	<u>mm Hg</u>
151.3	1
217.3	20
262.3	100
308	400
332	760

Solubilities at 25°C:

Solvent

ethanol	48 g/100 g solvent (WSSA, 1979)
ethyl ether	miscible (WSSA, 1979)
n-heptane	27 g/100 g solvent (WSSA, 1979)
toluene	miscible (WSSA, 1979)
xylene	miscible (WSSA, 1979)
water	0.0052 g/100 g solvent (WSSA, 1979)
water	50 ppm (Spencer, 1968; Kenaga, 1980)
water	100 ppm, technical product (BCPC, 1977)

Log P (octanol-water partition coefficient):

measured	2.297 (Rao and Davidson, 1982)
calculated	3.33 (Saarikoski and Viluk-sela, 1982)

pK_a value: 4.6 (Cessna and Grover, 1978)

Soil adsorption coefficient (Kenaga, 1980):

experimental	124
calculated	510

BCF calculated from (Kenaga, 1980):
water solubility
K_{oc}

68
6

Dinoseb is soluble in petroleum oil and organic solvents (BCPC, 1977; Spencer, 1968). It forms salts with inorganic and organic bases, some of which are readily soluble in water. Dinoseb thermally degrades at 180°C (Stojanovic et al., 1972).

1.3. PRODUCTION DATA

Dinoseb is prepared by the nitration of 2-sec-butylphenol, which is made by the reaction of butylene and phenol with separation of the 4-isomer (BCPC, 1977).

The following domestic companies are listed as producers of dinoseb (SRI, 1983; USITC, 1983a): Dow Chemical (Midland, MI); Vertac Chemical (Vicksburg, MS); Blue Spruce Co. (Bound Brook, NJ) and Uniroyal. Production of dinoseb in 1981 and 1980 was 11.6 and 12.2 million pounds, respectively (USITC, 1981, 1982). In 1982, 2.5 million pounds of dinoseb were imported into the United States (USITC, 1983b).

1.4. USE DATA

Dinoseb is used as a general purpose herbicide (WSSA, 1979; BCPC, 1977; Ouellette and King, 1977; Spencer, 1968). It can be used prior to planting, pre-emergence, postemergence and directed postemergence depending upon weed problem, crop or formulation. It can be applied on numerous crops, fruits and nuts. Recommended rates of application range from 0.75-12 lb/acre depending upon use conditions. Dinoseb has limited insecticide properties.

In 1982, 4.3 million pounds and 0.4 million pounds of dinoseb were used by American farmers on soybeans and peanuts, respectively, while use in 1976 was 3.7 and 0.3 million pounds, respectively (USDA, 1983). In 1975, an

estimated total of 6.2 million pounds of dinoseb were consumed domestically with use as follows: citrus, 0.1; deciduous fruits, 0.3; peanuts, 1.2; soybeans, 3.6; and vegetables, 1.0 million pounds.

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. WATER

The fate and transport of dinoseb in the aquatic environment has not been studied comprehensively. Like other herbicides, the fate of dinoseb in water will depend on its ability to undergo photochemical, chemical and biological reactions. Data specific to the photodecomposition of dinoseb in water were not located; however, UV spectra for the structurally-related herbicides DNAP (2-pentyl-4,6-dinitrophenol) and DNOCHP (2-cyclohexyl-4,6-dinitrophenol) (Gore et al., 1971) show that these herbicides absorb significant amounts of light in the environmentally significant spectra range (≥ 290 nm). Also, Thibeau et al. (1978) report that the absorption band maximum for dinoseb is 376 nm. This does not, however, predict photolysis rates or environmental importance. Plimmer (1980) noted that nitrophenol herbicides are susceptible to decomposition by UV irradiation in alkaline solutions. Ivie and Casida (1971) found that dinoseb could undergo photodecomposition on bean leaves and that the photolysis could be photosensitized (Section 2.3.).

Data regarding the water hydrolysis of dinoseb were not available. Gould and Weber (1976) reported the ozonolysis of dinoseb under conditions that could be produced at wastewater or drinking water treatment facilities. The addition of activated charcoal was found to retard the decomposition rate of dinoseb during ozonolysis.

Data presented in Section 2.3. show that microbial breakdown of dinoseb has been demonstrated by soil organisms. Therefore, microbial degradation of dinoseb in the aquatic environment may have some significance. An abstract of a Romanian study (Petre et al., 1970) indicates that dinoseb has

some resistance to biological degradation in water. At dinoseb concentrations up to 1 ppm, the maximum reduction was 30%, while at 25 ppm only 7% of the dinoseb was decomposed. Additionally, dinoseb was added to natural waters (0.5-0.6 ppm) and after 15 months of storage in the laboratory, the dinoseb remaining was 50-60% of the initial concentration.

Data specific to the transport of dinoseb from water that is due to volatilization or adsorption to sediments or suspended matter were not located. In a review article, Bailey and White (1964) reported that vapor losses of dinoseb are much greater from a wet soil than from a dry soil up to a 17% moisture level.

Kenaga (1980) predicted BCFs for dinoseb based upon its K_{oc} value and its water solubility to be 6 and 68, respectively. Compounds having BCFs <100 are considered unlikely to bioconcentrate.

2.2. AIR

Data specific to the fate and transport of dinoseb in the atmosphere were not located in the available literature. As noted in Section 2.1., dinoseb absorbs UV irradiation in environmentally significant wavelength ranges (>290 nm). However, the importance of photodegradation of dinoseb in the air has not been studied and cannot be accurately predicted.

2.3. SOIL

Analogous to the fate of dinoseb in water, the fate of dinoseb in the soils is determined by biological, photochemical and chemical reactions and transport processes. The ability of dinoseb to be degraded by microorganisms has been demonstrated by several investigators. Wallnoefer et al. (1978) showed that dinoseb was degraded by three strains of an Azotobacter species previously isolated from an agricultural soil. The Azotobacter,

which is a nitrogen fixing bacteria, decomposed the dinoseb into the transient metabolite 6-amino-2-sec-butyl-4-nitrophenol and then to the metabolite 6-acetamido-2-sec-butyl-4-nitrophenol. Williams (1977), in a review of pesticide metabolism by anaerobic microorganisms, reported that dinoseb undergoes degradation by rumen microbiota. The metabolites formed by the ruminal fluid were identified as 6-amino-2-sec-butyl-4-nitrophenol and 4,6-diamino-2-sec-butylphenol. Doyle et al. (1978) studied the effect of dairy manure and sewage sludge on dinoseb degradation in the soil. A silt loam soil was treated with dinoseb (5 ppm) and the effect of manure and sludge upon microbial respiration, $^{14}\text{CO}_2$ evolution, and distribution of ^{14}C in the degradation products, was measured. After 60 days in the laboratory at 25°C , 36.0% of the ^{14}C evolved as $^{14}\text{CO}_2$ in the control sample indicating microbial degradation in the untreated soil. Evolution of $^{14}\text{CO}_2$ in the manure and sludge samples was 31.1-35.1% and 17.8-19.8%, respectively, indicating that the rate of microbial degradation was retarded by the manure and sludge additions. Douros and Reid (1956) reported that decomposition of dinoseb in the soil is thought to be caused by Pseudomonas aeruginosa and P. putida; supporting evidence was not available from the reference source.

As noted in Section 2.1., dinoseb absorbs UV irradiation in environmentally significant ranges, indicating a potential for photodegradation. Ivie and Casida (1971) measured the photodecomposition of dinoseb on bean leaves and the effect of rotenone as a photosensitizer. The ^{14}C dinoseb was applied to the leaves at a concentration of 10 ppm and was immediately exposed to the sunlight for 1 hour. After 1 hour, 5.6% of the applied ^{14}C dinoseb was recovered as photodecomposition products. The addition of the rotenone photosensitizer, at levels of 10 ppm and 100 ppm, accelerated the photodecomposition rate from 5.6 to 9.4 and 21.1%, respectively.

Data specific to the chemical hydrolysis or other chemical reactions of dinoseb in the soil were not located in the available literature.

The transport loss of dinoseb from soil that is due to volatilization has been mentioned by WSSA (1979) and Bailey and White (1964). WSSA (1979) reported that some losses from steam distillation under specific conditions of soil acidity, high temperatures and surface soil moisture will occur. In a review article, Bailey and White (1964) reported that vapor losses of dinoseb have been found to be much greater from a wet soil than from a dry soil up to a soil moisture content of 17%. Above this 17% level, additional moisture appears to reduce the volatilization of the dinoseb. Also, increasing temperatures increase the vapor loss from soils.

The mobility (adsorption-leaching) of dinoseb in soils has been studied by several investigators. Harris (1967) measured the mobility of dinoseb in soil columns using a silty clay loam and a sandy loam. An arbitrary mobility scale was determined in which a value of 1.0 represented no movement in the soil and a value of 6.0 represented maximum movement. In the silty clay loam, the dinoseb had a mobility value of 4.2, while its value in sandy loam was 4.0. Kunze (1965) reported that dinoseb is not adsorbed on clay minerals present in the soil at pH 7.3; however, adsorption on these minerals increases significantly (to nearly 100%) as the pH is lowered to 4.6. Davis and Selman (1954) found that the water-soluble salts of dinoseb are more leachable than the oil-soluble dinoseb. WSSA (1979) reported that dinoseb is not tightly adsorbed on most agricultural soils and that it can leach in porous, sandy soils. However, experiments have demonstrated that for normal temperature zone rainfall and infiltration rates, dinoseb should not be leached from the top foot of soil by rainfall in the first year after application, during which time it is subjected to soil microbial degradation (WSSA, 1979).

Little information regarding the persistence of dinoseb in the soil is available in the literature. WSSA (1979) reports that the resultant average persistence of phytotoxicity at recommended application rates is 2-4 weeks under average conditions of use.

3. EXPOSURE

3.1. WATER

Frank et al. (1979) analyzed the water of 237 wells in Ontario, Canada, over the 10-year period 1969-1978, which were suspected of being contaminated by herbicides. The results of this study with respect to dinoseb are summarized in Table 3-1. Dinoseb was detected in a total of six wells. The authors traced the entry of dinoseb into the wells and these data are also given in Table 3-1. In one case, dinoseb was spilled in quantity around a well, and it soaked into the soil where it remained with little movement as long as the soil was moist to dry. However, during the spring thaw, the soil was saturated with water and the dinoseb leaked into the well.

The U.S. EPA STORET Data Base (see Appendix) reports the analysis of dinoseb in a total of 190 water samples. Dinoseb was detected in all 190 samples. The mean concentration of dinoseb in the water samples was reported to be $<1.13 \mu\text{g/l}$, with a range of $<1.0-25.0 \mu\text{g/l}$.

3.2. FOOD

Monitoring data identifying dinoseb as a contaminant in ready-to-eat foods were not located in the available literature. Cessna (1979) treated fababeans with preemergence applications of dinoseb (amine salt) and then analyzed the mature beans for residues. The maximum dinoseb residue detected was 8 ppb, with a detection limit of 2 ppb.

3.3. INHALATION

Pertinent data regarding exposure to dinoseb by inhalation were not located in the available literature.

3.4. DERMAL

Pertinent data regarding dermal exposure to dinoseb were not located in the available literature.

TABLE 3-1
Dinoseb Contamination of Ontario Well Water, 1969-1979*

Dinoseb Concentration Detected in Well ($\mu\text{g}/\text{L}$)	Number of Wells Contaminated	Reason for Contamination
0.01-0.1	2	drift during spraying
0.1-1.0	0	NA
1.1-10	1	storm runoff
11-100	1	storm runoff
101-1000	1	single or extended spill of diluted dinoseb
1001-1000	1	single or extended spill of concentrated dinoseb

*Source: Frank et al., 1979

NA = Not applicable

4. PHARMACOKINETICS

4.1. ABSORPTION

The absorption of dinoseb has been demonstrated in a variety of mammalian organisms. In the case of a fatal oral poisoning in man, dinoseb was found in the blood filtrate (Drabner et al., 1967). No other details were given.

Gibson and Rao (1973) investigated the absorption of dinoseb in mice. ^{14}C -dinoseb (uniformly ring-labeled) was administered either orally or i.p. to either pregnant (11th day of gestation) or nonpregnant females. Dinoseb was monitored by a colorimetric technique involving extraction with MEK, and dinoseb and its metabolites were monitored following the appearance of ^{14}C in the tissues and plasma. The ^{14}C associated with dinoseb itself was taken as the MEK-extractable material, while ^{14}C associated with unspecified metabolites was the material not extractable into MEK. For pregnant females, peak levels of ^{14}C -dinoseb were observed in the blood of the mother as well as in embryonic tissue within 8 minutes after a 17.7 mg/kg i.p. dose, and within 12 hours of a 32 mg/kg oral dose. Furthermore, embryonic levels of ^{14}C -dinoseb never exceeded 2.5% of maternal plasma levels, indicating the probable existence of a placental barrier. Metabolites of dinoseb were found in embryonic and maternal tissues but not in maternal blood. For nonpregnant females, the disparity between plasma levels of ^{14}C -dinoseb after oral and i.p. administration (same doses as in pregnant females) was also apparent. Based on mean values of dinoseb in plasma for groups of five mice, the rate constants for absorption were ~ 7 and 229 hour^{-1} for oral and i.p. administration, respectively.

Edgerton and Moseman (1978) detected the presence of dinoseb in the blood of mice that had been exposed orally to dinoseb incorporated in feed.

After 138 days of exposure at levels of either 40 or 160 ppm, values of dinoseb in the blood were reported as 15.4 or 39.7 ppm, respectively. Dinoseb was also found in the urine and feces of these mice, but the levels were only a fraction of those reported for blood (1-2 ppm).

A Polish scientist reported the presence of dinoseb in the blood of rats that had been exposed dermally to an unspecified acute dose of dinoseb (Henneberg, 1966). Seven hours after exposure, a chromatographic-spectrophotometric technique revealed a peak absorption value of 39% for dinoseb in the blood. This corresponded to an absolute value of 3.99-4.70 mg%. The rate of absorption was given as 0.38-0.83 mg/cm²/hour over a period of 24 hours.

These studies indicate that dinoseb is absorbed readily by the skin and gastrointestinal tracts of adult mammals, but probably not to a significant extent by embryos in situ.

4.2. DISTRIBUTION

The study by Edgerton and Moseman (1978), discussed in Section 4.1., indicated that dinoseb was found in the adipose tissue, brain, liver and blood of rats after 138 days of chronic oral exposure. The details can be found in Table 4-1. While the amount of dinoseb in adipose tissue and liver increased in proportion (~4-fold) to dose, there was only a 3-fold increase in the levels in blood and a 1.7-fold increase in the brain levels between the low- and high-dose groups. Similarly, the study by Gibson and Rao (1973) (see Section 4.1.) indicated that ¹⁴C-dinoseb and its metabolites were found in the blood, liver, kidneys, brain and embryo of pregnant mice 3 hours after either oral or i.p. administration (Table 4-2). After oral

TABLE 4-1
Dinoseb Recovery After 138 Days*

Sample	40 ppm Level	160 ppm Level	Control
Adipose	0.88	3.46	<0.1
Brain	0.70	1.16	<0.1
Liver	0.29	1.06	<0.1
Blood	15.40	39.70	<0.1

*Source: Edgerton and Moseman, 1978

TABLE 4-2
Recovery of Dinoseb and Its Metabolites After Oral or
Intraperitoneal Administration to Pregnant Mice^a

Tissue	Mean Tissue Level ^b (μg/g of Dinoseb and Its Metabolites)			
	Total ^c		Dinoseb Alone ^d	
	Oral (32 mg/kg)	Intraperitoneal (17.7 mg/kg)	Oral (32 mg/kg)	Intraperitoneal (17.7 mg/kg)
Blood	31.3 ± 5.4	45.0 ± 1.4	29.7 ± 4.6	46.6 ± 3.9
Liver	26.5 ± 4.1	32.9 ± 1.3	14.2 ± 0.6	15.6 ± 1.8
Kidney	21.8 ± 3.9	28.6 ± 4.4	13.8 ± 1.4	15.4 ± 1.4
Embryo	2.1 ± 0.2	5.1 ± 0.4	1.8 ± 0.1	2.9 ± 0.0

^aSource: Gibson and Rao, 1973

^bBased on molecular weight of dinoseb

^cBased on total radioactivity

^dMeasured as MEK-extractable material

Values are means ± SEM (n = ≥3)

administration, dinoseb was distributed to total body water (0.66 ± 0.13 g/kg), while after i.p. administration, dinoseb was distributed to extracellular water (0.18 ± 0.18 g/kg) (Gibson and Rao, 1973). Though a specific value for dinoseb found in brain tissue was not reported, these authors suggested that it was similar to the values found in embryos, indicating the existence of a blood-brain barrier.

Furthermore, Russian investigators reported in an abstract that dinoseb exhibited affinity for receptor sites in human serum albumin (Luik and Luk'yanchuk, 1981), and that the extent of binding might be an indicator of toxicity; low levels of toxicity would be associated with low affinity for the receptor site (Luik et al., 1983). They also reported that dinoseb is "high capacity/low affinity" with respect to binding to serum albumin (Luk'yanchuk and Luik, 1983), and that in rats, sulfonamides might interfere with the binding of dinoseb to serum albumin (Luk'yanchuk and Luik, 1981). However, no information regarding doses or other details was available from these abstracts.

The observation that dinoseb binds to plasma proteins was also reported by Froeslie and Karlog (1970) for ruminants. After gastric exposure to an unspecified dose, 95% of the absorbed dinoseb was bound to plasma proteins.

4.3. METABOLISM

In the study by Henneberg (1966) discussed in Section 4.1., O-amino-p-nitrophenol was detected after dermal exposure of rats to dinoseb. No other details were given.

From an in vitro study involving the incubation of an unspecified amount of dinoseb with either rat caecal contents or human Escherichia coli for 1-5 days at 37°C, Fujita et al. (1982) identified the primary metabolites of dinoseb (by thin layer chromatography and infrared and mass spectrometry) as 6-amino-4-nitro-2-sec-butylphenol, 6-acetylamino-4-nitro-2-sec-butylphenol.

These investigators reported that the primary metabolism of dinoseb involves a reduction of the nitro group to an amino group, and N-acetylation of the amino group (Fujita et al., 1982).

Froeslie and Karlog (1970) and Froeslie (1971) reported that dinoseb, when incubated anaerobically at a concentration of ~190 µg/ml in the ruminal fluid of a cow, was first reduced to 6-amino derivatives and subsequently to diamino compounds. Reduction of dinoseb to diamino compounds failed to occur when the fluid had been heat sterilized, indicating that microflora are necessary for the metabolism of dinoseb to occur. They also reported that high initial concentrations, $1-4 \times 10^{-2}$ M, inhibited the metabolism of dinoseb. Under in vivo conditions, the reduction of dinoseb to diamino compounds was complete within 1 hour. Again, details were not given.

Similarly, Ingebrigtsen and Froeslie (1980) reported the ultimate degradation of dinoseb to diamino compounds in rat caecal contents. Incubation of the caecal contents with an unspecified concentration of dinoseb was for 24 hours, and metabolites were determined spectrophotometrically. The degradation took place in <2 hours.

4.4. EXCRETION

After 138 days of chronic oral exposure to dinoseb at either 40 or 160 ppm in the diet, rats excreted dinoseb in the urine and feces. The values reported for both urine and feces were 1-2 ppm and did not appear to be dose-related (Edgerton et al., 1978).

The study by Gibson and Rao (1973) (see Section 4.1.) indicated that 67-78% of the radioactivity from an administered dose of ^{14}C -dinoseb was recovered in the urine and feces of mice within 64 hours, regardless of the route of administration (gavage or i.p. administration). However, the route

of administration affected the rate of excretion into the feces; this is due to differences in biliary excretion. The rate of elimination of ^{14}C -dinoseb and metabolites by the embryo paralleled the rate of elimination of ^{14}C -dinoseb from the plasma of the adult; in both cases, elimination was first order. After oral administration, the rate of elimination was 0.02 hour^{-1} , whereas i.p. administration yielded an elimination value of 0.09 hour^{-1} .

5. EFFECTS

5.1. CARCINOGENICITY

The relationship between exposure to herbicides and the presence of malignant mesenchymal soft tissue tumors in humans was reported in a case control study by Eriksson et al. (1979). The respective frequencies of exposure to dinoseb for tumor patients (n=110) and their matched controls (n=219) were 2.7 and 0.9%. Hardell et al. (1980, 1981) reported the incidence of exposure to various chemicals in patients with malignant lymphomas and their matched controls. The frequency of exposure to dinoseb was 0.6% in patients (n=169) and 0% in matched controls (n=355). This difference was not statistically significant.

In a chronic exposure study, Innes et al. (1969) found dinoseb not to be tumorigenic in mice exposed by gavage to the maximally tolerated dose (2.15 mg/kg/day) of dinoseb from days 7-28 of age followed by maintenance on diets containing 7 ppm of dinoseb for ~18 months. Eighteen males and 18 females from each of two strains [(C57BL/6 x C3H/Anf)_{F₁} and (C57BL/6 x AKR)_{F₁}] were treated with dinoseb, exposed to positive control substances (7 total), or used as negative controls. After ~18 months of treatment or nontreatment, all mice were sacrificed and examined for tumors. Thoracic and abdominal cavities but not the cranial cavity were dissected and examined. Histological evaluation was performed on all major organs and on any visible lesions. Blood smears were taken before sacrifice and examined only in cases where splenomegaly or lymphadenopathy were apparent. Mice treated with dinoseb and compared with untreated controls were found not to have a statistically significant (0.1 level of significance) increase in the numbers of any type of tumor regardless of sex or strain.

5.2. MUTAGENICITY

The mutagenic effects of dinoseb are summarized in Tables 5-1 and 5-2. The bulk of the data indicates that while dinoseb failed to produce mutations in prokaryotic and eukaryotic systems, it displayed interactions with both DNA and RNA in eukaryotes as well as prokaryotes.

Reverse mutation assays performed with various strains of his-requiring Salmonella typhimurium (Eisenbeis et al., 1981; Simmon et al., 1976; Waters et al., 1982; Andersen et al., 1972), rII mutants of phage T₄ (Andersen et al., 1972), and a tryptophane auxotroph strain of Escherichia coli (Waters et al., 1982) gave consistently negative results. A forward mutation assay with phage T₄ (Andersen et al., 1972) and a study involving a sex-linked recessive lethal in Drosophila melanogaster also gave negative results for dinoseb.

Assays involving sperm morphology yielded conflicting results. In a study where mice were exposed to 20 mg/kg/day dinoseb either intraperitoneally or by gavage for 5 days, no significantly different numbers of abnormal sperm were detected relative to untreated controls 35 days after treatment (Osterloh et al., 1983). In another study, Linder et al. (1982) reported that rats exposed orally to 9.1, 15.6 or 22.2 mg/kg/day dinoseb for 11 weeks displayed abnormal sperm after the 11th week at the 9.1 and 15.6 levels and after 20 days at the 22.2 level. Rats exposed to 3.8 mg/kg/day for 11 weeks displayed no higher percentages of abnormal sperm than did untreated controls. Values of percent normal sperm after 11 weeks of treatment were given as 95, 46 and 25 for 3.8, 9.1 and 15.6 mg/kg/day levels, respectively, and 2-3% after 20 days for the 22.2 mg/kg/day level. Furthermore, of the rats allowed a 16-week recovery period after 11 weeks of exposure to dinoseb, only those exposed to 9.1 mg/kg/day showed signs of remission with

TABLE 5-1

Mutagenicity Assays Performed With Dinoseb

Assay	Species	Strain	Concentration/ Dose	Application Method or Route of Administration	Activation System	Response	Comments	Reference
Reverse mutation	<u>Salmonella</u> <u>typhimurium</u>	TA1535, TA1537, TA1538, TA98, TA100	10 μ g/plate	plate incorporation	+/-	-	NC	Eisenbeis et al., 1981
Reverse mutation	<u>S.</u> <u>typhimurium</u>	5 his-requiring strains	NR	NR	+/-	-	NC	Simon et al., 1976
Reverse mutation	<u>S.</u> <u>typhimurium</u>	TA1535, TA1537, TA1538, TA98, TA100	10 mg/plate	plate incorporation	+/-	-	NC	Waters et al., 1982
Reverse mutation	<u>S.</u> <u>typhimurium</u>	8 his-requiring strains	1-5 μ g/plate	plate incorporation	-	-	NC	Andersen et al., 1972
Forward mutation	phage T ₄	wild type	1-5 μ g/plate	liquid incubation	-	-	NC	Andersen et al., 1972
Reverse mutation	phage T ₄	AP72, M17	1-5 μ g/plate	liquid incubation	-	-	NC	Andersen et al., 1972
Reverse mutation	<u>Escherichia</u> <u>coli</u>	WP2	10 mg/plate	plate incorporation	+/-	-	NC	Waters et al., 1982
Sex-linked recessive lethal	<u>Drosophila</u>	NR	NR	NA	NA	-	NC	Waters et al., 1982
Sperm morphology	mouse	(C57BL/6 x C3H) F ₁	20 mg/kg/day x 5 days	Intraperitoneal or by gavage	NA	-	Epididymal sperm were ana- lyzed by light microscopy 35 days after treatment	Osterloh et al., 1983
Sperm morphology	rat	Sherman	3.8 mg/kg/day 9.1 mg/kg/day 15.6 mg/kg/day 22.2 mg/kg/day	oral	NA	- + + +	Epididymal sperm were ana- lyzed by light microscopy after 11 weeks of treatment for 3.8-15.6 mg/kg dose levels, and after 10, 20, 30 and 50 days for the 22.2 mg/kg level. Percent normal sperm for 3.8, 9.1 and 15.6 mg/kg levels were 95, 46 and 25, respectively. After 20 days, there were 2% normal sperm at the 22.2 mg/kg level.	Linder et al., 1982

NA = Not applicable; NC = no comment; NR = not reported

TABLE 5-2
Interactions of Dinoseb With DNA or RNA

Assay	Species	Strain	Method of Application	Dose	Activation System	Results	Comments	Reference
Relative toxicity	<i>Escherichia coli</i>	repair-deficient and proficient	NR	NR	+	+	NC	Simon et al., 1976
Relative toxicity	<i>Bacillus subtilis</i>	repair-deficient and proficient	NR	NR	-	+	NC	Simon et al., 1976
pol A/A- differential toxicity	<i>E. coli</i>	p3476 (pol A-) M3100 (pol A+)	spot test	NR	-	+	NC	Waters et al., 1982
Rec A/A- differential toxicity	<i>B. subtilis</i>	M45 (rec A-) H17 (rec A+)	spot test	NR	-	+	NC	Waters et al., 1982
Rec+/rec- differential toxicity	<i>S. typhimurium</i>	SL4700 (rec-) SL452 (rec+) TA1978 (uvrB+) TA1538 (uvrB-)	spot test	NR	-	+	NC	Waters et al., 1982
Mitotic gene conversion	<i>Saccharomyces cerevisiae</i>	a/alpha, ade 2-0/ ade 2-1 his1-1/ his1-7	plate incorporation	185-1665 ppm	-	+	ade-2 prototrophs reached a maximum at ~740 ppm (600/10 ⁶ survivors); his-1 prototrophs reached a maximum at ~1295 ppm (~55/10 ⁶ survivors)	Parry, 1973
Mitotic gene conversion	<i>S. cerevisiae</i>	NR	NR	NR	+	-	Details not reported in this abstract	Simon et al., 1976
Unscheduled DNA synthesis	human lung fibroblast	WI-38	tissue culture	NR	+/-	-	NC	Waters et al., 1982

NC = No comment

NR = Not reported

regard to abnormal sperm morphology (93% normal). Rats exposed to 15.6 mg/kg/day displayed an average value of 66% after 16 weeks of recovery. All rats exposed to 22.2 mg/kg/day for the purpose of assessing sperm morphology were killed after 11 weeks; recovery data therefore were not available for this treatment group.

A preponderance of studies indicated that dinoseb interacted with DNA. These included the following: 1) relative toxicity assays where growth of repair-deficient strains of Escherichia coli and Bacillus subtilis was compared with that of repair-proficient strains (Simmon et al., 1976); 2) a relative toxicity assay where growth of a DNA polymerase I-deficient strain of Escherichia coli was compared with that of a DNA polymerase I-containing strain (Waters et al., 1982); and 3) relative toxicity assays where growth of recombination-deficient strains of Salmonella typhimurium and Bacillus subtilis was compared with that of recombination-proficient strains (Waters et al., 1982).

Two studies that evaluated mitotic gene conversion in Saccharomyces cerevisiae gave conflicting results. Waters et al. (1982) reported that treatment with dinoseb caused an increase in the numbers of ade-2 and his-I prototrophs. Maxima were achieved at ~740 and 1295 ppm dinoseb for ade-2 and his-I, respectively. In a similar study, Simmon et al. (1976) reported no effect of dinoseb, although no details were provided in the available literature.

Waters et al. (1982) measured unscheduled DNA synthesis in human fibroblasts treated with dinoseb, fibroblasts treated with compounds known to produce unscheduled DNA synthesis, and fibroblasts treated with DMSO, a negative control. Dinoseb caused no significant increase in unscheduled DNA synthesis relative to the negative control.

5.3. TERATOGENICITY

Data concerning the teratogenicity of dinoseb are summarized in Table 5-3. In general, the data indicate that dinoseb was significantly teratogenic only when administered intraperitoneally or subcutaneously, but not when administered orally.

Gibson (1973) administered dinoseb to pregnant mice by oral, subcutaneous or i.p. routes on days 10-12, 14-16 or 8-16 of gestation. Sublethal doses ranged from 0-17.7 mg/kg/day for mice treated intraperitoneally or subcutaneously, or from 0-32 mg/kg/day for mice treated orally. Fetuses were examined for size, weight, soft tissue anomalies and skeletal anomalies on day 19 of gestation. Fetuses of animals treated intraperitoneally with dinoseb at 17.7 mg/kg/day were smaller and displayed a significant incidence of soft tissue and skeletal anomalies with respect to those of untreated controls, particularly when mothers were treated on days 10-12 of gestation. No effects were observed at a treatment level of 5 mg/kg/day when dinoseb was administered intraperitoneally. Similar effects were observed when dinoseb was administered subcutaneously; however, the no-effect level was 10 mg/kg/day for this route of administration. When administered orally, dinoseb had no significant effect on fetal survival, weight or tissue development. There was a reduction, however, (not statistically significant) in the crown-rump length at the 32 mg/kg/day level. The no-effect level for oral administration of dinoseb was 20 mg/kg/day. Kavlock and Chernoff (1980) reported in an abstract that dinoseb was not teratogenic to mice treated in an unspecified manner at doses equal to either LD_{10} or LD_{40} on day 8 of gestation. However, they reported an increased incidence (52%) of an extra rib in the fetuses of dinoseb-treated animals fed the highest dose.

TABLE 5-3

Teratogenicity of Dinoseb

Route	Species/ Strain	No. Dams at Start	Vehicle	Daily Dose (mg/kg)	Treatment Days	Observation Days	Maternal Response	Fetal Response	Reference
i.p. Injection	mice/ Swiss- Webster	8	water	0	10-12	19	No. deaths = 1, 5 and 4 at 17.7, 18.8 and 20 mg/kg/day doses. Hyperthermia in 17.7-20 mg/kg/day groups. There were no deaths at the lower doses.	Smaller animals. Sig- nificant incidences of soft tissue and skele- tal anomalies in 17.7- 20 mg/kg treatment groups. No effects observed at lower doses.	Gibson, 1973
		11		10					
		7		12.5					
		7		15.8					
		14		17.7					
s.c. Injection	mice/ Swiss- Webster	11	water	18.8	14-16	19	No. deaths = 0, 0 and 4 at the 0, 12.5 and 17.7 mg/kg/day levels, respectively	Greater % of resorption smaller fetuses at 12.5 and 17.7 mg/kg/day levels.	Gibson, 1973
		4		20					
		7		0					
		7		12.5					
		12		17.7					
Oral Intubation	mice/ Swiss- Webster	7	water	5.0	8-16	19	No effect.	No effect.	Gibson, 1973
		7		0					
		7		10					
		7		17.7					
		8		0					
Oral Intubation	mice/ Swiss- Webster	8	water	10	14-16	19	Hyperthermia at 17.7 mg/kg/day treatment levels.	Smaller fetuses and greater percent resorp- tion at 17.7 mg/kg. Statistically signifi- cant gross or soft tissue anomalies at 17.7 mg/kg/day.	Gibson, 1973
		8		17.7					
		5		0					
		8		10					
		8		17.7					
Oral Intubation	mice/ Swiss- Webster	6	water	0	8-16	19	100% survival except for 17.7 mg/kg level on days 14-16 (one death).	Skeletal anomalies at 17.7 mg/kg/day level. No deaths on fetuses from dams given 10 mg/kg/day.	Gibson, 1973
		8		20					
		8		32					
		8		50					
		14		20					
Oral Intubation	mice/ Swiss- Webster	11	water	32	10-12	19	No. deaths = 0, 0, 0 and 6 at 0, 20, 32 and 50 mg/kg/day levels. Unspecified maternal toxicity at all levels of treatment.	No significant effect on fetal size or sur- vival.	Gibson, 1973
		11		32					
Oral Intubation	mice/ Swiss- Webster	14	water	20	14-16	19	No. deaths = 0 and 2 at 0 and 30 mg/kg/day levels. Unspecified toxicity.	No significant effect on fetal size or sur- vival.	Gibson, 1973
		11		32					

TABLE 5-3 (cont.)

Route	Species/ Strain	No. Dams at Start	Vehicle	Daily Dose (mg/kg)	Treatment Days	Observation Days	Maternal Response	Fetal Response	Reference
Oral intubation (cont.)		8 9		20 30	8-16	19	No deaths = 1 and 2 at 20 and 32 mg/kg levels, respectively. Unspecified toxicity.	Fetal crown-rump dis- tance reduced at 32 mg/kg level.	Gibson, 1973
NR	mice	NR	NR	LD ₁₀ or LD ₄₀	8	18	NR	No effect on fetal viability. No terata. Increased incidence of extra rib (52%) in high-dose group.	Kavlock and Chernoff, 1980
1-p. injection	rat/ Sprague- Dawley	12 6 10 16 6 6 4	saline	0 6.3 8.0 9.0 11.2 12.5 15.8	10-12	21 of gestation or at 1, 7 or 42 post-partum	No survivors beyond the 9.0 mg/kg level of treatment. 20% mortality at 9 mg/kg level. 100% survival at levels <9 mg/kg.	No effect on no. of fetuses, but fetuses weighed significantly less at 8 and 9 mg/kg levels. No difference in weight was observed at 42 days post-partum. Vacuolated and necrotic livers at the 8 and 9 mg/kg levels through 42 days post-partum. No effect on heart or lungs. Kidneys and dilated tubules and excessive mesenchymal tissues at 8 and 9 mg/kg level in fetuses. Ureters were also dilated at these levels. The incidence of these afflictions was re- duced or absent by 42 days post-partum. Renal trans- port was not affected at any level of treatment.	McCormack et al., 1980
1-p. injection	rat/ Mistar	82 control 11 treated	corn oil	10	9-10	Embryos taken either 24 hours after day 9 treatment or 4 hours after day 10 treatment and cultured either 24 or 42 hours.	NR	Day 9: significant delays in axial rota- tion, neural tube closure. No delays in anterior bud formation or somite formation. Analysis were also con- ducted after 42 hours in culture, but low survivorship made mean- ingful statistical analysis impossible. Day 10: few embryos were affected	Beaudoin and Fisher, 1981

NR = Not reported

McCormack et al. (1980) reported that 21-day-old fetuses of rats treated by i.p. injection with 8 or 9 mg/kg/day dinoseb on days 10-12 of gestation displayed abnormalities in kidney morphology and lesions of the liver, and weighed significantly less than controls. However, offspring of treated mothers examined at 42 days postpartum displayed only hepatic lesions. Furthermore, dinoseb had no apparent effect on the transport function of kidneys in these fetuses.

Beaudoin and Fisher (1981) monitored the development of embryos taken from rats treated intraperitoneally with dinoseb (10 mg/kg/day). Embryos taken 4 hours after maternal treatment and grown 24 hours in culture displayed no developmental delays. However, embryos taken 24 hours after treatment and grown 24 hours in culture showed significant delays in axial rotation and neural tube closure, but no delays in the other variables that were measured.

Various studies also suggested that the teratogenic effects of intra-peritoneally administered dinoseb might be enhanced if mothers were placed in environmentally stressing situations (i.e., heat or food deprivation) (Preache and Gibson, 1974a,b, 1975).

5.4. OTHER REPRODUCTIVE DATA

Dose levels of 15.6 and 22.2 mg/kg/day dinoseb produced histological changes in the testes of rats (20 animals/treatment group) fed dinoseb for 11 weeks (Linder et al., 1982). These changes included abnormal spermatozoa and spermatids, and damage to spermatogenic cells. Animals at these levels also had reduced sperm counts and suffered reproductive failure (i.e., despite a "normal" numbers of mating attempts, no litters were sired by these males within a 2-week post-treatment period). After a post-treatment recovery period of 16 weeks there was little or no remission of these

effects. Decreased epididymal sperm counts and some testicular changes were observed in male rats exposed to doses of 9.1 mg/kg/day dinoseb for 11 weeks, but these animals did not suffer reproductive failure, and any changes observed in testes morphology or sperm count were absent after a 16-week post-treatment recovery period. No testicular or reproductive effects of dinoseb were observed in animals treated with 3.8 mg/kg/day.

In the study performed by Osterloh et al. (1983) (see Section 5.2.), male mice treated intraperitoneally with 20 mg/kg/day dinoseb had neither reduced sperm counts nor decreased testicular weights when examined 35 days after treatment.

Decidualized pseudopregnant rats were fed dinoseb on days 6-9 of pseudopregnancy (Spencer, 1981). On day 10, uterine protein, uterine glycogen, uterine water and ovarian protein were analyzed in an unspecified manner. Uterine water was reduced at a dose of 750 ppm, uterine protein and glycogen were "reduced" in rats fed ≥ 5 ppm, and ovarian protein was "diminished" at doses < 50 ppm.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

Male Sherman rats were observed during 11 weeks of oral treatment with dinoseb at dose levels of 0, 3.8, 9.1, 15.6 or 22.2 mg/kg/day (see Section 5.4.). Males receiving 15.6 or 22.2 mg/kg/day lost weight rapidly, and after 11 weeks sustained average weight losses of 19 and 38%, respectively. When treatment was stopped, the rats treated at the lower level of dose ultimately regained their original weights, while rats receiving the higher dose failed to attain their original weights within 16 weeks. Rats given 9.1 mg/kg/day maintained a constant weight throughout treatment, and rats receiving 3.8 mg/kg/day gained weight in a manner similar to untreated controls. Rats receiving 9.1, 15.6 and 22.2 mg/kg/day displayed increased food consumption with respect to controls by the 4th week of treatment.

Body temperature was elevated significantly throughout the period of treatment only in rats fed 15.6 or 22.2 mg/kg/day dinoseb. Rats exposed to these higher levels of dinoseb also displayed atypical sprawling postures, profuse salivation, and rapid, irregular breathing. The reproductive effects associated with dinoseb in this study have been discussed in Sections 5.2. and 5.4. (Linder et al., 1982). No other parameters were investigated.

In a Romanian study, mice were exposed orally to dinoseb at a level of 1 mg/kg/day for 90 days, and rats were exposed orally to the same level of dinoseb for 210 days (Petre and Calciu, 1973). In this study, dinoseb stimulated hepatic succinic dehydrogenase activity for both mice and rats, stimulated growth in rats, and had no effect on growth in mice. However, experimental data were not given in this abstract.

Isac et al. (1981) reported that rats exposed "chronically and acutely" to 750 or 1000 mg/kg dinoseb in an unspecified manner, for an unspecified length of time, showed petit mal eleptiform activity in an EEG, but no change in an ECG.

5.6. OTHER RELEVANT INFORMATION

Dinoseb is reported to have a wide range of effects upon mammalian systems. Gorny and Miszczak (1981) reported that rats exposed in an unspecified manner to 6.6 mg/kg dinoseb had increased amounts of acetylcholine in the cerebral cortex, but that synthesis of acetylcholine was reduced. No other information was given in this translation from Polish. Another Polish scientist reported that dinoseb inhibited the caseinolytic and fibrinolytic activity of plasman. No other details were given (Skrzydlewski, 1972). Other abstracts reported that dinoseb inhibited horseradish peroxidase-catalyzed oxidative decarboxylation of tryptophane (Scarponi et al., 1980); had "effects" on the CNS in rats exposed in an unspecified

manner to doses $>0.3 \text{ LD}_{50}$ (Pawlowski, 1970); promoted methemoglobinemia in goats, sheep and pigs exposed intraruminally (Froeslie, 1971; Ingebrigtsen and Froeslie, 1980); possibly promoted changes in levels of liver enzymes and proteins in rats exposed orally to 0.4-4 mg/kg (Dimitriu and Isac, 1981); and reduced hematopoietic functions (fewer erythrocytes and lower mean total cellularity of spleen, thymus and lymph nodes) in mice exposed orally to doses of 24-48 $\mu\text{g/g}$ every 3 days for 30 days (Springer et al., 1979).

Dinoseb was also reported to suppress both cellular and humoral immune response in mice treated orally with an acute dose equal to 0.5 LD_{50} (Dandlicker et al., 1980). Burkatskaya (1970), however, reported that dinoseb had no effects on levels of beta and gamma globulins in the blood of rats 4-10 days after treatment with an unspecified oral dose.

Under in vitro conditions, dinoseb was shown to be an uncoupler of oxidative phosphorylation in mitochondria isolated from livers and brains of mice (Ilivicky and Casida, 1969). Under in vivo conditions, however, dinoseb failed to exhibit uncoupling. The mitochondria isolated from livers and brains of mice injected intraperitoneally with 63 $\mu\text{M/kg}$ ($\text{LD}_{50} = 42 \mu\text{M/kg}$) dinoseb were not significantly different from those isolated from untreated controls, with respect to uncoupling of oxidative phosphorylation.

A case of suspected poisoning with dinoseb in man was reported by Smith (1981). After a day of spraying crops, symptoms included chest and abdominal pain, excessive thirst, intermittent fever, shortness of breath, insomnia, loss of appetite, patchy areas in the lungs and impaired liver function. These symptoms disappeared after 10-12 weeks (Smith, 1981).

Various LD_{50} values have been reported for dinoseb. These are reported in Table 5-4.

6. AQUATIC TOXICITY

6.1. ACUTE EFFECTS

The acute lethal levels of dinoseb have been determined for several species of freshwater fish (Table 6-1). Salmonid species (trout and salmon) appear to be the most sensitive to dinoseb exposure, having static 96-hour LC_{50} values between 44 and 110 $\mu\text{g}/\text{l}$ (ppb). The median lethal levels for the guppy and channel catfish were also near the upper range of that in trout. Lethal levels in the lake trout were ~3 times higher when tests were conducted at 5°C instead of 10°C, but temperature did not appear to affect the toxicity of dinoseb to cutthroat trout (Johnson and Finley, 1980). Increased alkalinity of the test solutions was associated with decreased toxicity (higher LC_{50} values) in guppies (Saarikoski and Viluksela, 1961), cutthroat and lake trout (Johnson and Finley). At pH 6.0, 7.0 and 8.0, the 96-hour LC_{50} values in the guppy were 106, 353 and 985 μg dinoseb/l, respectively. In the trout, an increase in alkalinity from pH 6.5 to 8.5 caused as much as a 30-fold increase in median lethal levels. Flowthrough testing conditions apparently decreased the toxicity of dinoseb to trout, since Johnson and Finley (1980) noted that the "time-independent LC_{50} values" (the toxicant concentration at which 50% of the animals could survive indefinitely) were 54 and 102 $\mu\text{g}/\text{l}$ for lake and cutthroat trout, respectively. Both values are higher than the static 96-hour LC_{50} values determined for these species.

Several studies have reported lethal levels of dinoseb for aquatic crustaceans. Dinoseb was quite toxic to larval lobsters, Homarus americanus, having a lethal threshold value of 7.5 $\mu\text{g}/\text{l}$ (Zitko et al., 1976). Adult lobsters were less sensitive, with a 96-hour lethal threshold near 300 $\mu\text{g}/\text{l}$. In comparison, the freshwater crayfish was quite resistant,

TABLE 6-1

Acute Lethal Effects of Dinoseb to Freshwater Fish

Species	Duration (hours)	Concentration ($\mu\text{g}/\text{L}$)	Method	Effect	Reference
Coho salmon, <u>Oncorhynchus kisutch</u>	24 144	190 88	static; 10°C static; 10°C	LC50 LC50	Spehar et al., 1981
Cutthroat trout, <u>Salmo clarki</u>	96 TI	67 102	static; 10°C flowthrough	LC50 LC50	Johnson and Finley, 1980
Lake trout, <u>Salmo namaycush</u>	96 TI	44 54	static; 10°C flowthrough	LC50 LC50	Johnson and Finley, 1980
Coho salmon, <u>Oncorhynchus kisutch</u>	96	100	static; 10°C	LC50	Lorz et al., 1979
Atlantic salmon, <u>Salmo salar</u>	96	70	static; 9°C	lethal threshold	Zitko et al., 1976
Speckled trout, <u>Salvelinus fontinalis</u>	24 96	180 110	NS NS	LC50 LC50	Christie and Penney, 1972
Channel catfish, <u>Ictalurus punctatus</u>	96	118	static; 21°C	LC50	McCorkle et al., 1977
Guppy, <u>Poecilia reticulata</u>	96 96 96	106 353 985	static; pH 6.0 static; pH 7.0 static; pH 8.0	LC50 LC50 LC50	Saarikoski and Viluksela, 1981

TABLE 6-1 (cont.)

Species	Duration (hours)	Concentration (µg/g)	Method	Effect	Reference
Harlequin fish, <u>Rasbora heteromorpha</u>	24	3400b	Intermittent replacement	LC50	Alabaster, 1969
	48	3400b	Intermittent replacement	LC50	
Golden orfe, <u>Leuciscus idus</u>	NS	1060	NS	nonlethal	Juhnke and Luedsmann, 1978
	NS	2000	NS	50% lethality	
	NS	3000	NS	100% lethality	

aMedian concentration of that causing 50% mortality and the highest concentration causing no mortality

bActive ingredient was 9% of test formulation

NS = Not specified

TI = Time independent; toxicant levels at which 50% of the animals would be expected to survive indefinitely

0560p

-34-

07/23/84

Luk'yanchuk, V.D. and A.I. Luik. 1983. Pesticide toxicity and affinity to albumin in the process of pesticide biotransformation. Zh. Iksp. Klin. Med. (Rus.) 23(1): 33-38. (CA 098/211187C)

McCorkle, F.M., J.E. Chambers and J.D. Yarborough. 1977. Acute toxicities of selected herbicides to fingerling channel catfish, Ictalurus punctatus. Bull. Environ. Contam. Toxicol. 18(3): 267-270.

McCormack, K.M., A. Abuelgasim, V.L. Sanger and J.B. Hook. 1980. Postnatal morphology and functional capacity of the kidney following prenatal treatment with dinoseb in rats. J. Toxicol. Environ. Health. 6(3): 633-644.

McLeese, D.W., V. Zitko and M.R. Peterson. 1979. Structure-lethality relationships for phenols, anilines and other aromatic compounds in shrimp and clams. Chemosphere. 8(2): 53-57.

Noakes, D.W. and D.M. Sanderson. 1969. Determining the dermal toxicity of pesticides. Br. J. Ind. Med. 26(1): 64-69.

Osterloh, J., G. Letz, S. Pond and C. Becker. 1983. An assessment of the potential testicular toxicity of 10 pesticides using the mouse-sperm morphology assay. Mutat. Res. 116(3-4): 407-415.

Ouellette, R.P. and J.A. King. 1977. Chemical Week Pesticides Register. McGraw-Hill Book Co., New York. p. 1982.

0560p

-48-

03/15/85

surviving 215 and 144 hours, respectively, at 1000 and 10,000 $\mu\text{g/l}$ with no toxic effects. McLeese et al. (1979) reported that the 96-hour LC_{50} for the marine shrimp, Crangon septemspinosus, was 5100 $\mu\text{g/l}$. In the freshwater scud, Gammarus fasciatus, the 24-, 48- and 96-hour LC_{50} values were 2800, 2500 and 1800 $\mu\text{g dinoseb/l}$ (Sanders, 1970).

In the marine molluscan clam, Mya arenaria, the lethal threshold for 84 hours of exposure was 2600 $\mu\text{g/l}$ (McLeese et al., 1979).

6.2. CHRONIC EFFECTS

Pertinent data regarding the effects of chronic dinoseb exposure to aquatic species were not located in the literature. Kenaga (1982), however, reported that based on MATC values for fathead minnows and lake trout, the ACR ranged from 27-167. Assuming an acute toxicity (96-hour LC_{50}) of ~ 100 $\mu\text{g/l}$ for these fish (see Table 6-1), the MATC would therefore be < 5.0 $\mu\text{g dinoseb/l}$.

6.3. PLANT EFFECTS

The effects of dinoseb on algal species have been reported by several investigators. Bringmann and Kuhn (1977, 1978) reported that the toxicity threshold for the green algae, Scenedesmus quadracauda, was 1.3 mg dinoseb/l. Toxicity was determined turbidimetrically as the inhibition of cell multiplication over an 8-day period. In the blue-green alga, Microcystis aeruginosa, cell multiplication was inhibited at 5.7 mg dinoseb/l at pH 7.0 (Bringmann and Kuhn, 1978). Tubea (1980) and Tubea et al. (1981) exposed Chlorella pyrenoidosa (green alga) and Lyngbya birgei (blue-green alga) to dinoseb at 24, 240 and 2400 $\mu\text{g/l}$ under various test conditions for 72 and 48 hours, respectively. Dinoseb did not affect the growth of Chlorella (determined photometrically) at the concentrations tested.

Lyngbya growth was decreased at levels $>240 \mu\text{g/l}$, most notably in high-nitrogen and high-calcium media. Growth in Lyngbya was 84 and 41% of controls at 240 and 2400 $\mu\text{g/l}$, respectively (Hawxby et al., 1977). The green alga, Chlorococcum sp., and the blue-green alga, Anabaena sp., were not affected by dinoseb at levels up to 2400 $\mu\text{g/l}$ for 24 hours (Hawxby et al., 1977). Petrea (1980) reported that photosynthesis was stimulated in Chlorella vulgaris at 50-1000 $\mu\text{g/dinoseb/l}$ (72-hour exposure) and respiration was increased at 5000 $\mu\text{g/l}$ (24-hour exposure). Petre et al. (1970) also reported that dinoseb at 25 mg/l stimulated water flora but was inhibitory at 100 mg/l.

Dinoseb was found to have a fairly high affinity for binding to the thylakoid membranes of the green alga, Ankistrodesmus braunii (Laasch et al., 1981, 1982). These authors suggested, however, that this binding did not cause growth inhibition.

6.4. RESIDUE

In an English abstract of a Romanian study, Petre et al. (1970) reported that dinoseb in water had a high resistance to biological degradation. Although times for degradation were not reported, 30 and 7%, respectively, of 1 and 25 mg dinoseb/l had degraded.

6.5. OTHER RELEVANT INFORMATION

Additional data regarding the toxicity of dinoseb to aquatic species were not located in the available literature.

7. EXISTING GUIDELINES

7.1. HUMAN

A tolerance of 0.1 ppm (negligible residue) has been established by U.S. EPA for residues of dinoseb in or on grains, fruits, vegetables, forage and hay, while 1 ppm is the tolerance level in or on soybean forage and hay (Code of Federal Regulations, 1982; Federal Register, 1983). An odor threshold of 0.032 mg/l for dinoseb in water at 60°C has been suggested as a result of studies performed by Alexander et al. (1982).

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of dinoseb were not located in the available literature.

8. RISK ASSESSMENT

No evidence of carcinogenicity was found in two strains of mice treated orally with dinoseb in a chronic study (Innes et al., 1969). The human case-control studies discussed in Section 5.1. (Eriksson et al., 1979; Hardell et al., 1980) provide little insight into the relationship between cancer and exposure to dinoseb.

Dinoseb was not mutagenic when tested in a variety of assays involving prokaryotes and eukaryotes, but did exhibit interaction with DNA in both prokaryotic and eukaryotic systems. Sperm morphology studies in rodents yielded conflicting results with respect to the mutagenic effects of dinoseb.

Dinoseb was significantly teratogenic in rats only when administered intraperitoneally or subcutaneously. Teratogenicity was not demonstrated in rats exposed orally to dinoseb (Gibson, 1973).

Only one detailed subchronic study (Linder et al., 1982) was found in the available literature. As discussed in Sections 5.4. and 5.5., rats exposed orally to either 15.6 or 22.2 mg/kg/day dinoseb for 11 weeks experienced weight loss, increased food consumption, elevated body temperatures and reproductive failure resulting from testicular changes. After a 16-week post-treatment period, the rats exhibited remission of weight change, food consumption and body temperature effects, but little or no remission of reproductive effects. A no-effect level of 3.8 mg/kg/day was established in this study. This study was too narrow in focus and of insufficient duration (77 days) for use as the basis of an ADI for humans.

Statements concerning available literature in this document refer to published, quotable sources and are in no way meant to imply that confidential data, which this document could not address, are not in existence.

These data, which are Confidential Business Information (CBI), are available in summary form as a CBI Appendix that can be accessed by individuals with appropriate clearance. Conclusions from the CBI Appendix regarding risk assessment, however, can be presented in this chapter.

The CBI Appendix to this document reviews other animal data from which an ADI of 0.001 mg/kg/day or 0.07 mg/day for a 70 kg man is derived. Since a NOAEL could not be defined, the ADI was based on a LOAEL of 1 mg/kg/day for decreased body weight in spite of increased food consumption and for decreased thyroid weight in rats in a 2-year feeding study and an uncertainty factor of 1000.

9. REFERENCES

- Alabaster, J.S. 1969. Survival of fish in 164 herbicides, insecticides, fungicides, wetting agents, and miscellaneous substances. *Int. Pest. Control.* 11(2): 29-35.
- Alexander, H.C., W. M. McCarty, E.A. Bartlett and A.N. Syverud. 1982. Aqueous odor and taste threshold values of industrial chemicals. *J. Am. Water Works. Assoc.* 74(11): 595-599.
- Andersen, K.J., E.G. Leighty and M.T. Takahashi. 1972. Evaluation of herbicides for possible mutagenic properties. *J. Agric. Food Chem.* 20: 649-656.
- Bailey, G.W. and J.L. White. 1964. Review of adsorption and desorption of organic pesticides by soil colloids, with implications concerning pesticide bioactivity. *J. Agric. Food Chem.* 12: 324-332.
- Bailey, G.W. and J.L. White. 1965. Herbicides: A compilation of the IR, physical, chemical, and biological properties. *Res. Rev.* 10: 97-123.
- BCPC (British Crop Protection Council). 1977. Dinoseb. In: *Pesticide Manual*, 5th ed., H. Martin and C.R. Worthing, Ed. BCPC Publications, Worcestershire, England. p. 210, 593.
- Beaudoin, A.R. and D.L. Fisher. 1981. An in vivo/in vitro evaluation of teratogenic action. *Pestab.* 23(1): 57-61.

- Bringmann, G. and R. Kuhn. 1977. Limiting values for the damaging action of water pollutants to bacteria (Pseudomonas putida) and green algae (Scenedesmus quadricauda) in the cell multiplication inhibition test. S. Wasser Abwasser Forsch. (Ger.) 10(3-4): 87-98.
- Bringmann, G. and R. Kuhn. 1978. Testing of substances for their toxicity threshold: Model organisms Microcystis (Diplocystis) aeruginosa and Scenedesmus quadricauda. Mitt. Int. Ver. Theor. Angew. Limnol. 21: 275-284.
- Burkatskaya, E.N. 1970. Toxicology of nitrophenol pesticides. Vop. Gig. Toksikol. Pestits. (Rus.) p. 121-124. (CA 21/110893d)
- Cessna, A.J. 1979. Determination of the herbicide dinoseb in fababeans. J. Agric. Food Chem. 27(1): 191-193.
- Cessna, A.J. and R. Grover. 1978. Spectrophotometric determination of dissociation constants of selected herbicides. J. Agric. Food Chem. 26: 289-292.
- Christie, P.M.P. and G.H. Penney. 1972. Preliminary results of bioassays to determine the toxicity of some agricultural pesticides used in the Maritimes area. Environ. Can. Res. Develop. Br. 72: 2. (Cited in Zitko et al., 1976)
- Code of Federal Regulations. 1982. Dinoseb; tolerances for residues. 40 CFR 180.281.

- Dandliker, W.B., A.N. Hicks, S.A. Levinson, K. Stewart and R.J. Brawn. 1980. Effects of pesticides on the immune response. *Environ. Sci. Technol.* 14(2): 204-210.
- Davis, F.L. and F.L. Selman. 1954. Effects of water upon the movement of dinitro weed killers in soils. *Weeds*. 3: 11-20. (CA 49: 2009d)
- Dimitriu, G. and M. Isac. 1981. Effect of industrial dinoseb in carboxymethylcellulose (CMC) suspension on tissue proteins and dehydrogenase function in liver. (*Rum.*) 27(2a): 99-101. (CA 096/137471f)
- Douros, J.D., Jr. and J.J. Reid. 1956. Decomposition of certain herbicides by soil microflora. *Bacterial. Proc.* 23 p.
- Doyle, R.C., D.D. Kaufman and G.W. Burt. 1978. Effect of dairy manure and sewage sludge on ¹⁴C-pesticide degradation in soil. *J. Agric. Food Chem.* 26(4): 987-989.
- Drabner, J., H.M. Kuehnert and W. Schwerd. 1967. Detection of dinoseb in blood and organs in poisoning with Gebutox liquid. *Arch. Toxicol.* (Ger.) 22(5): 390-395. (CA 17/79552W)
- Edgerton, T.R. and R.F. Moseman. 1978. Electron-capture gas chromatographic determination of 2-sec-butyl-4,6-dinitrophenol (DNBP) residues in feed, tissue, and excreta. 1978. *J. Agric. Food Chem.* 26(2): 425-528.

- Eisenbels, S.J., D.L. Lynch and A.E. Hampel. 1981. The Ames mutagen assay tested against herbicides and herbicide combinations. *Soil Sci.* 131(1): 44-47.
- Eriksson, M., N.O. Berg, L. Hardell and T. Moller. 1979. Case control study of malignant mesenchymal soft-tissue tumors and exposure to chemical substances. *Lakartidningen.* (Swe.) 76(4): 3872-3875. (Taken from PESTAB 80/0738)
- Federal Register. 1983. Tolerances for pesticide chemicals in or on raw agricultural commodities; dinoseb. *Federal Register.* 48(43): 9004. (CA 98:141993)
- Frank, R., G.J. Sirons and B.D. Ripley. 1979. Herbicide contamination and decontamination of well waters in Ontario, Canada, 1969-1978. *Pestic. Monit. J.* 13(3): 120-127. (CA 92: 141784v)
- Froeslie, A. 1971. Ruminal metabolism and methemoglobin-forming effect of dinobuton (2-(1-methyl-n-propyl)-4,6-dinitrophenyl isopropyl carbonate) in sheep. *Acta. Vet. Scand.* 12(2): 300-302. (CA 17/109109S)
- Froeslie, A. and O. Karlog. 1970. Ruminal metabolism of DNOC (4,6-dinitro-o-cresol) and DNBP (4,6-dinitro-2-sec-butylphenol). *Acta. Vet. Scand.* 11(1): 114-132. (CA 17/853434)
- Fujita, M., M.A. Mori, T. Miyahara and H. Kosuka. 1982. Metabolism of 4,6-dinitro-2-sec-butylphenol by rat fecal contents and human strains of Escherichia coli. (Jap.) 28(2): 89-93. (Taken from HEEP/83/04700)

Gibson, J.E. 1973. Teratology studies in mice with 2-sec-butyl-4,6-dinitrophenol (dinoseb). Food Cosmet Toxicol. 11: 31-43.

Gibson, J.E. and K.S. Rao. 1973. Disposition of 2-sec-butyl-4,6-dinitrophenol (dinoseb) in pregnant mice. Food Cosmet. Toxicol. 11: 45-52.

Gore, R.C., R.W. Hannah, S.C. Pattacini and T.J. Porro. 1971. Infrared and ultraviolet spectra of seventy-six pesticides. J. Assoc. Off. Anal. Chem. 54(5): 1040-1057.

Gorny, D. and M. Miszczak. 1981. Brain level and synthesis of acetylcholine during exposure to vibration and organic-phosphorus and phenol-derived pesticides. Acta. Physiol. Pol. 32(4): 469-476. (Taken from HEEP/83/00314)

Gould, J.P. and W.J. Weber, Jr. 1976. Oxidation of phenols by ozone. J. Water Pollut. Control Fed. 48(1): 47-60.

Hardell, L., M. Eriksson and P. Lenner. 1980. Maligna lymfom och exposition foer kemiska substanser, saerskilt organiska loeningsmedel, klorfenoler och fenoxysyror. (Malignant lymphoma and exposure to chemical substances, especially organic solvents, chlorophenols, and phenoxy acids.) Lakartidningen (Swe.) 77(4): 208-210. (Taken from PESTAB Abstr. 80/1309)

Hardell, L., M. Eriksson, P. Lenner and E. Lundgren. 1981. Malignant lymphoma and exposure to chemicals, especially organic solvents, chlorophenols and phenoxy acids: A case controlled study. Br. J. Cancer. 43: 169-176.

- Harris, C.I. 1967. Movement of herbicides in soil. *Weeds*. 15: 214-216.
- Hawxby, K., B. Tubea, J. Ownby and E. Basler. 1977. Effects of various classes of herbicides on four species of algae. *Pestic. Biochem. Physiol.* 7(3): 203-209.
- Henneberg, M. 1966. Cutaneous absorption of 4,8-dinitro-2-secbutylphenol and 4,6-dinitro-2-isopropylphenol in rats. *Acta. Pol. Pharm. (Pol.)* 23(4): 371-378. (CA 1/1784h)
- Ilivicky, J. and J.E. Casida. 1969. Uncoupling action of 2,4-dinitrophenols, 2-trifluoromethylbenzimidazoles, and certain other pesticide chemicals upon mitochondria from different sources and its relation to toxicity. *Biochem. Pharmacol.* 18(6): 1389-1401.
- Ingebrigtsen, K. and A. Froeslie. 1980. Intestinal metabolism of 4,6-dinitro-o-cresol and 2-(1-methyl-n-propyl)-4-6-dinitrophenol in the rat. *Acta Pharmacol Toxicol.* (46(5): 326-328.
- Innes, J.R.M., B.M. Ulland, M.G. Valerio, et al. 1969. Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: A preliminary note. *J. Natl. Cancer Inst.* 42: 1101-1114.
- Isac, M., G. Dimitriu and R.M. Isac. 1981. Functional changes in white rats acutely and chronically poisoned by industrial dinoseb. *An. Stiint. (Rum.)* 27: 121-127. (CA 96/137492q)

- Ivie, G.W. and J.E. Casida. 1971. Photosensitizers for the accelerated degradation of chlorinated cyclodienes and other insecticide chemicals exposed to sunlight on bean leaves. *J. Agric. Food Chem.* 19(3): 410-416.
- Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. U.S. Dept. of the Interior, Fish and Wildlife Service. Resource Publ. 137.
- Juhnke, I. and D. Luedemann. 1978. Results of the study of 200 chemical compounds on acute fish toxicity using the Golden Orfe test. *Z. Wasser Abwasser Forsch.* (Ger.) 11(5): 161-164.
- Kavlock, R.J. and N. Chernoff. 1980. Effects of acute maternal toxicity upon fetal development in the mouse. *Teratology.* 21: 48A.
- Kenaga, E.E. 1980. Predicted bioconcentration factors and soil sorption coefficients of pesticides and other chemicals. *Ecotoxicol. Environ. Safety.* 4: 26-38.
- Kenaga, E.E. 1982. Predictability of chronic toxicity from acute toxicity of chemicals in fish and aquatic invertebrates. *Environ. Toxicol. Chem.* 1(4): 347-358.
- Kunze, G.W. 1965. Pesticides and clay minerals. *In: Pesticide Effect. Soil Water Symp.*, PAP, Columbus, OH. p. 49-70.

- Laasch, H., K. Pfister and W. Urbach. 1981. Comparative binding of photosystem II herbicides to isolated thylakoid membranes and intact green algae. *Z. Naturforsch., C: Biosci.* 36C(11-12): 1041-1049.
- Laasch, H., K. Pfister and W. Urbach. 1982. High- and low-affinity binding of photosystem II herbicides to isolated thylakoid membranes and intact algal cells. *Z. Naturforsch., C: Biosci.* 37C(7-8): 620-631.
- Linder, R.E., T.M. Scotti, D.J. Svendsgaard, W.K. McElroy and A. Curley. 1982. Testicular effects of dinoseb in rats. *Arch. Environ. Contam. Toxicol.* 11(4): 475-485.
- Lorz, H.W., S.W. Glenn, R.H. Williams, C.M. Kunkel, L.A. Norris and B.R. Loper. 1979. Effects of Selected Herbicides on Smolting of Coho Salmon. U.S. EPA, ORD, Duluth, MD. 103 p. EPA 600/3-79-071.
- Luik, A.I. and V.D. Luk'yanchuk. 1981. Changes of toxicity and level of affinity to human albumin during metabolism of toxicants. *Dopov. Akad. Nauk Ukr. RSR. (Ukr.)* 11: 77-79. (CA 096/099050H)
- Luik, A.I., V.D. Luk'yanchuk, O.I. Lebed, A.V. Stefanov and A.E. Boldeskul. 1983. Affinity for serum albumin as an index of the biological activity of xenobiotics. *Otkl. Akad. Nauk SSSR. (Rus.)* 268(2): 488-492. (CA 098/138632N)
- Luk'yanchuk, V.D. and A.I. Luik. 1981. Increased risk of poisoning with dinitrophenol pesticides during use of sulfanilamide drugs. *Gig. TR Prof. Zabol. (Rus.)* 0(8): 49-50. (Taken from HEEP/82/12490)

- Parry, J.M. 1973. The induction of gene conversion in yeast by herbicide preparations. *Mutat. Res.* 21: 83-91.
- Pawloski, L. 1970. Effect of dinitrobutylphenol on the higher nervous activity in experimental animals. *Med. Pracy. (Pol.)* 21(4): 349-358. (CA 19/97810c)
- Petre, I. and A. Calciu. 1973. Experimental study of pesticides which display high persistence in water. *Igiena.* 22(2): 83-92. (Rum.) (CA 79/143385W)
- Petre, I., I. Filipidescu and S. Branga. 1970. Persistence and toxicity of the Dibutox pesticide in water. *Igiena.* (Rum.) 19(9): 539-550. (CA 74: 124022)
- Petrea, V. 1980. Effect of the pesticide Dibutox on the physiological processes of algae Chlorella vulgaris. *Stud. Cercet. Biol., Ser. Biol. Veg.* (Rum.) 32(1): 73-76. (CA 93:180884)
- Plimmer, J.R. 1980. Herbicides. *In: Kirk-Othmer Encyclopedia of Chemical Technology*, 3rd ed., M. Grayson and D. Eckroth, Ed. John Wiley and Sons, Inc., New York. p. 332-334.
- Preache, M. and J.E. Gibson. 1974a. Enhancement of dinoseb-induced teratogenicity by maternal food deprivation in mice. *Toxicol. Appl. Pharmacol.* 29: 122. (Taken from ETIC/74/001740)

Preache, M.M. and J.E. Gibson. 1974b. Alteration of dinoseb-induced toxicity and teratogenicity in mice by environmental stress conditioning. Pharmacologist. (Taken from ETIC/74/029135)

Preache, M.M. and J.E. Gibson. 1975. Effects in mice of high and low environmental temperature on the maternal and fetal toxicity of 2-sec-butyl-4,6-dinitrophenol (dinoseb) and on disposition of ^{14}C -dinoseb. Teratology. 12: 147-156. (Taken from ETIC/75/008183)

Rao, P.S.C. and J. M. Davidson. 1982. Retention and transformation of selected EMS: A critical review. U.S. EPA, Athens, GA. EPA 600/33-82-060.

Saarikoski, J. and M. Viluksela. 1981. Influence of pH on the toxicity of substituted phenols to fish. Environ. Contam. Toxicol. 10(6): 747-753.

Saarikoski, J. and M. Viluksela. 1982. Relation between physicochemical properties of phenols and their toxicity and accumulation in fish. Exotox. Environ. Safety. 6: 501-512.

Sanders, O. 1970. Toxicities of some herbicides to six species of freshwater crustaceans. J. Water Pollut. Control Fed. 42(8): 1544-1550.

Scarponi, L., F. Tafuri and P. Perucci. 1980. Effects of certain herbicides on the oxidative decarboxylation of tryptophan by peroxidase. Pestic. Sci. 11(4): 446-450. (CA 11/782929)

Simmon, V.F., D.C. Poole and G.W. Newell. 1976. In vitro mutagenic studies of twenty pesticides. *Toxicol. Appl. Pharmacol.* 37: 109.

Skrzydlewski, Z., S. Kreczko, A. Mical and J. Skrzydlewska. 1972. Effect of certain derivatives of dinitroalkylphenols on trypsin, plasmin, and thrombin activities. *Med. Pr. (Pol.)* 23(3): 259-263. (CA 1699V)

Smith, W.D.L. 1981. An investigation of suspected dinoseb poisoning after the agricultural use of a herbicide. *Practitioner.* 225(1356): 923-926.

Spehar, R.L., A.E. Lemke, Q.H. Pickering, T.H. Roush, R.C. Russo and J.D. Yount. 1981. Effects of pollution on freshwater fish. *J. Water Pollut. Control Fed.* 53(6): 1028-1076.

Spencer, E.Y. 1968. *Guide to the Chemicals Used in Crop Protection*, 5th ed., Publ. 1093. Canada Dept. of Agriculture, Research Branch. p. 224.

Spencer, F. 1981. Effects of postimplantation exposure to selected pesticides on reproductivity in rats. NTIS PB 81-213209. (CA 096/001743P)

Springer, O., L. Skrinjar and A. Bunarevic. 1979. Effect of dinitrobutyl phenol on the lymphatic and hemopoietic tissues and organs. Presented at the 11th Congress of the Union of Physiological Societies of Yugoslavia, Prinstina, Yugoslavia, September. (Scr.) (Taken from HEEP/81/10499)

SRI (Stanford Research Institute). 1983. 1983 Directory of Chemical Producers: United States of America. SRI International, Menlo Park, CA. p. 779.

- Stojanovic, B.J., F. Hutto, M.V. Kennedy and F.L. Shuman, Jr. 1972. Mild thermal degradation of pesticides. J. Environ. Qual. 1(4): 397-401.
- Thibeau, R.J., L. Van Haverbeke and C.W. Brown. 1978. Detection of water pollutants by laser excited resonance Raman spectroscopy; pesticides and fungicides. Appl. Spectrosc. 32: 98-100.
- Tubea, B.I. 1980. The effects of nutrient, pH and herbicide levels on algal growth. Pestab. 40(10): 4596.
- Tubea, B., K. Hawxby and R. Mehta. 1981. The effects of nutrient, pH and herbicide levels on algal growth. Hydrobiol. 79(3): 221-227.
- USDA (U.S. Department of Agriculture). 1983. Inputs Outlook and Situation. USDA, Economics Research Service, Washington, DC. p. 9, 11. IOS-2, October.
- U.S. EPA/NIH (U.S. Environmental Protection Agency/National Institute of Health). 1983. OHMTADS. November, 1983: on line.
- USITC (United States International Trade Commission). 1981. Synthetic Organic Chemicals. U.S. Production and Sales, 1980. USITC, Washington, DC. p. 231. USITC Publ. 1183.
- USITC (United States International Trade Commission). 1982. Synthetic Organic Chemicals. U.S. Production and Sales, 1981. USITC, Washington, DC. p. 211. USITC Publ. 1292.

USITC (United States International Trade Commission). 1983a. Synthetic Organic Chemicals. U.S. Production and Sales, 1982. USITC, Washington, DC. p. 228. USITC Publ. 1422.

USITC (United States International Trade Commission). 1983b. Imports of Benzenoid Chemicals and Products, 1982. USITC, Washington, DC. p. 95. USITC Publ. 1401.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold, New York. p. 570.

Wallnoefer, P.R., W. Ziegler, G. Engelhart and H. Rothmeier. 1978. Transformation of dinitrophenol herbicides by Azotobacter sp. Chemosphere. 7(12): 967-972.

Waters, M.D., S.S. Sandhu and V.F. Simmon. 1982. Study of pesticide genotoxicity. Basic Life Sci. 21: 275-326.

Williams, P.P. 1977. Metabolism of synthetic organic pesticides by anaerobic microorganisms. Residue Rev. 66: 63-135.

WSSA (Weed Society of America). 1979. Dinoseb. In: Herbicide Handbook of the Weed Science Society of America, 4th ed. WSSA, Champaign, IL. p. 173-177.

Zitko, V., D.W. McLeese, W.G. Carson and H.E. Welch. 1976. Toxicity of alkyl dinitrophenols to some aquatic organisms. Bull. Environ. Contam. Toxicol. 16(5): 508-515.

APPENDIX
LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
MEDLINE
RTECS
SCI SEARCH
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE

These searches were conducted in November, 1983. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7th), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation, 1981, 1982, 1983). Cincinnati, OH. 486 p.

ACGIH (American Conference of Governmental Industrial Hygienists). 1983. TLVs: Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1983-1984. Cincinnati, OH. 94 p.

BCPC (British Crop Protection Council). 1977. Pesticide Manual, 5th ed., H. Martin and C.R. Worthing, Ed. British Crop Protection Council. 593 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2A. John Wiley and Sons, NY. 2878 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2B. John Wiley and Sons, NY. 2879-3816 p.

Clayton, G.D. and F.E. Clayton, Ed. 1982. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2C. John Wiley and Sons, NY. 3817-5112 p.

- Grayson, M. and D. Eckroth, Ed. 1978-1983. Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. John Wiley and Sons, NY. 23 Volumes.
- Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Inc., MA. 575 p.
- ITII (International Technical Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. 700 p.
- NTP (National Toxicology Program). 1983. Carcinogenesis Testing Program. Chemicals on Standard Protocol. Management Status.
- Ouellette, R.P. and J.A. King. 1977. Chemical Week Pesticide Register. McGraw-Hill Book Co., NY.
- Sax, I.N. 1979. Dangerous Properties of Industrial Materials, 5th ed. Van Nostrand Reinhold Co., NY.
- SRI (Stanford Research Institute). 1983. Directory of Chemical Producers. Menlo Park, CA.
- U.S. EPA. 1982. Chemical Activities Status Report, 3rd ed. (EPACASR). Offices of Pesticides and Toxic Substances, Washington, DC. EPA 560/TIIS-82-002b.
- U.S. EPA. 1983. Status Report on Rebuttable Presumption Against Registration (RPAR) or Special Review Process. Registration Standards and the Data Call In Programs. Office of Pesticide Programs, Washington, DC.
- U.S. EPA. 1983. CHIB Existing Chemical Assessment Tracking System. Name and CAS Number Ordered Indexes. Office of Toxic Substances, Washington, DC.
- USITC (United States International Trade Commission). 1983. Synthetic Organic Chemicals. U.S. Production and Sales, 1982. Washington, DC. USITC Publication 1422.
- Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY.